

Variant: *NM_000156.6(GAMT):c.497T>C (p.Leu166Pro)*

Version: 2.0

CA402994573 [↗](#)

1312506 (ClinVar) [↗](#)

Gene: GAMT ([HGNC:2593](#))

Condition: guanidinoacetate methyltransferase deficiency
([MONDO:0012999](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: c194f442-bf68-499f-8e16-8f525d10b3a1

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HGVS expressions

NM_000156.6:c.497T>C

NM_000156.6(GAMT):c.497T>C (p.Leu166Pro)

NC_000019.10:g.1398989A>G

CM000681.2:g.1398989A>G

NC_000019.9:g.1398988A>G

CM000681.1:g.1398988A>G

NC_000019.8:g.1349988A>G

NG_009785.1:g.7565T>C

ENST00000252288.8:c.497T>C

ENST00000447102.8:c.497T>C

ENST00000591788.3:c.180T>C

ENST00000640164.1:n.330T>C

ENST00000640762.1:c.428T>C

ENST00000252288.6:c.497T>C

ENST00000447102.7:c.497T>C

ENST00000591788.2:c.182T>C

NM_000156.5:c.497T>C

NM_138924.2:c.497T>C

NM_138924.3:c.497T>C

Pathogenic

Met criteria codes **5**

PP3_Strong

PS3_Supporting

PP4_Strong

PM2_Supporting

PM3_Supporting

Evidence Links **0**

Expert Panel

Cerebral Creatine Deficiency Syndromes VCEP [↗](#)

Criteria Specification Information

[↗](#) **Criteria Specification:** ClinGen Cerebral Creatine Deficiency Syndromes Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GAMT Version 1.1.0

[↗](#) **Criteria Specification Approval History**

[↗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Cerebral Creatine Deficiency Syndromes VCEP

The NM_000156.6:c.497T>C variant in GAMT is a missense variant predicted to cause substitution of leucine by proline at amino acid 166 (p.Leu166Pro). This variant has been detected in one individual with absent creatine peak on brain MRS, elevated guanidinoacetate and low creatine in urine, and decreased fibroblast GAMT activity (<5% normal); full GAMT gene sequencing was performed (PMID: 17186272, 17466557, 24268530, 24415674) (PP4_Strong). This individual was homozygous for the variant (0.5pts, PM3_Supporting) (PMID: 24268530, PMID: 17466557, PMID: 17186272). The highest population minor allele frequency in gnomAD v4.1.0. is 8.475e-7 (1/1179994 alleles) in the European non-Finnish population, which is lower than the ClinGen CCDS VCEP’s threshold for PM2_Supporting (<0.0004), meeting this criterion (PM2_Supporting). Expression of the variant in GAMT-deficient human fibroblast cell line resulted in <5% wild type GAMT activity indicating that this variant may impact protein function (PMID: 24415674) (PS3_Supporting). The computational predictor REVEL gives a score of 0.953 which is above the threshold of 0.932, evidence that correlates with impact to GAMT function at the strong level (PMID: 36413997) (PP3_Strong). There is a ClinVar entry for this variant (Variation ID: 1312506). In summary, this variant meets the criteria to be classified as pathogenic for GAMT deficiency based on the GAMT-specific ACMG/AMP criteria applied, as specified by the ClinGen Cerebral Creatine Deficiency Syndromes Variant Curation Expert Panel (Specifications Version 2.0.0): PP3_Strong, PP4_Strong, PS3_Supporting, PM2_Supporting, PM3_Supporting (Classification approved by the ClinGen Cerebral Creatine Deficiency Syndromes Variant Curation Expert Panel on December 10, 2025)

Met criteria codes

PP3_Strong			The computational predictor REVEL gives a score of 0.953 which is above the threshold of 0.932, evidence that correlates with impact to GAMT function at the strong level (PMID: 36413997) (PP3_Strong).
PS3_Supporting			PMID: 24415674: Expression of the variant in GAMT-deficient human fibroblast cell line resulted in <5% wild type GAMT activity indicating that this variant may impact protein function (PS3_Supporting)
PP4_Strong			One patient showed absent creatine peak on brain MRS, elevated urine guanidinoacetate and low creatine, and decreased fibroblast GAMT activity; full GAMT gene sequencing was performed (PMID: 17186272, 17466557, 24268530, 24415674).
PM2_Supporting			The highest population minor allele frequency in gnomAD v4.1.0. is 8.475e-7 (1/1179994 alleles) in the European (non-Finnish) population, which is lower than the ClinGen CCDS VCEP’s threshold for PM2_Supporting (<0.0004), meeting this criterion (PM2_Supporting).
PM3_Supporting			1 hom patient (PMID: 24268530)

Curation History 

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